

Topics in Primary Care Medicine

Screening Mammography

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Breast cancer is the most commonly occurring cancer in women and, until recently surpassed by lung cancer, was the leading cause of cancer-related death in women. It is the leading cause of death in women aged 39 to 44 years. The American Cancer Society has estimated that there will be 135,000 new cases of breast cancer and 42,300 breast cancer-related deaths in 1988. It is now predicted that breast cancer will develop in one out of every ten women in the United States. Given the clinical and public health significance of breast cancer, annual screening with mammography and clinical breast examination is recommended for women aged 50 and older to reduce breast cancer mortality.

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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The incidence of breast cancer in the United States is one of the highest in the world, and it is increasing, particularly in women younger than 40 years. Various factors have been proposed to explain changes in the breast cancer incidence, including changes in childbearing patterns, diet, the hormonal milieu, and increased detection. While epidemiologic studies have identified risk factors for breast cancer, the disease is so common that all women should be considered at risk. The American Cancer Society estimates that 75% of breast cancers will occur in women without known risk factors.

In the absence of dramatic improvements in survival for a given breast cancer stage and lacking methods that might prevent the disease, attention has been directed toward the early detection of breast cancer with the intent of finding curable disease and improving survival. Though many factors, including age, menopausal status, hormone receptor status, tumor histology, and cellular kinetics, are important determinants of survival, the tumor stage at diagnosis is the most widely used and perhaps the most important prognostic factor at this time. Because the tumor stage at diagnosis is an important determinant of survival and randomized clinical trials have shown that mortality from breast cancer can be reduced with screening, the early detection of breast cancer by aggressive screening has been recommended. The methods of screening include breast self-examination, clinical breast examination, and mammography. While the evidence concerning the effectiveness of breast self-examination in screening is mixed, there is strong evidence for the effectiveness of clinical breast examination and mammography in detecting earlier stages of breast cancer and

reducing mortality. Because the recommendations regarding mammography have been somewhat controversial and its use much less than recommended, this discussion will focus on the use of mammography in screening asymptomatic women for breast cancer.

The attributes of a good screening test include high sensitivity, high specificity, good patient and physician acceptance, low risk, and relative cost-effectiveness. A disease suitable for screening must have certain characteristics. These include a relatively prevalent detectable preclinical phase, serious consequences, and, an important factor, the disease must have a treatment that is more effective when applied to screening-detected disease than when applied to symptom-detected disease. An effective screening test should improve either survival, the quality of life, or both.

Several studies regarding the effectiveness of mammography as a screening test have shown that mammography prolongs survival and reduces the mortality from breast cancer. The first randomized clinical trial of mammography was the Health Insurance Plan of Greater New York (HIP) study, which in 1964 enrolled 62,000 women aged 40 to 64. At ten years of follow-up, this study showed a 30% reduction in breast cancer mortality among the study group of 32,000 women offered screening with an annual mammogram and clinical breast examination over four consecutive years, as compared with controls who continued to receive their usual medical care. At 14 years of follow-up (10 years after the last screening), the reduction in breast cancer mortality was 20% (118 deaths versus 153). These findings are even more remarkable given that they reflect the mortality reduction of the entire group offered screening, of which only two thirds ever

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ABBREVIATIONS USED IN TEXT

ACP = American College of Physicians
 BCDDP = Breast Cancer Detection Demonstration Project
 HIP = Health Insurance Plan [of Greater New York Study]

participated in the study. Both clinical breast examination and mammography independently contributed cases not detected by the other. Of the breast cancers detected in the screened women, a third were detected by mammography only, and 79% of cases detected by mammography only had normal axillary nodes at a surgical procedure. In the control group, 48% of the cases had normal axillary nodes at the operation. The screening benefit was initially thought to be primarily in women between ages 50 and 59, but subsequent HIP analyses have shown that the reduction in mortality extends to screened women in all enrolled age groups (40 to 64 years).

A more recent Swedish randomized trial of single-view mammography alone every 24 to 33 months in 163,000 women aged 40 to 74 showed a 31% decrease in mortality in the population offered screening (acceptance 89%) as compared with controls receiving their usual medical care. In the age group 50 to 74, the decrease in mortality was 40%. The screened population had a 25% reduction in stage II and in more advanced breast cancer. After year 7, this study showed a reduced mortality in the 40- to 49-year age group. These results are similar to those from the HIP study.

The Breast Cancer Detection Demonstration Project (BCDDP) was a voluntary screening program involving more than 280,000 women aged 35 to 74 years. Though the study lacked a control group, it showed a substantial decrease in the stage of breast cancer at diagnosis when mammography and clinical breast examination were combined. In this study, mammography detected 95% and clinical breast examination 33% of all breast cancers. Mammography alone detected 42% of all breast cancers, of which a third were found in women between ages 40 and 49. Furthermore, 70% of all screening-detected cases had normal axillary nodes. The BCDDP showed five- and ten-year relative survival rates of 88% and 79%, respectively, in the 4,240 women with histologically confirmed breast cancer. This improvement in overall survival and in survival in various disease subcategories was also seen in women diagnosed with breast cancer before age 50.

Two case-control studies from the Netherlands also have confirmed the effectiveness of mammography in screening for breast cancer. The Nijmegen study, involving 30,000 women who received single-view mammography alone every two years, showed a mortality reduction of 50% in the screened versus the unscreened population. This risk reduction extended to all age groups. The Utrecht project enrolled 14,796 women aged 50 to 64 and evaluated clinical breast examination and mammography. Using an age-matched control group, the risk of dying from breast cancer in those screened was 70% less than in those never screened.

Several other studies have shown the effectiveness of mammography in detecting early breast cancer and reducing mortality. Studies in which only single-view mammography was used as a preliminary screen or in which the screening interval was 24 to 33 months have shown a reduced mortality in the screened women. Its effectiveness has also been established in women younger than 50 years. Therefore, there is

substantial evidence supporting the use of mammography as a screening procedure.

While studies show that mammography is effective, it is also important to understand the limitations of the test and the clinical implication of these limitations. Due to variations in technology and the distribution of disease in screened populations, the reported sensitivity of mammography ranges from 60% to 94% and the specificity from 88% to 99%. The predictive value will vary with the prevalence or prior probability of the disease and sensitivity and specificity of the test. In the screening setting, the positive predictive value of mammography ranges from 10% to 35% and the negative predictive value generally is greater than 95%. The clinical significance of these statistics is that for each breast cancer diagnosed by mammography, there will be a number of false-positives that also require evaluation. The number of false-positive tests will vary with the prevalence of breast cancer—that is, as women age, the prevalence of breast cancer increases and the proportion of false-positive tests decreases. Similarly, when the prior probability of disease is high, the proportion of false-positive tests decreases. The ratio of biopsies with malignant to those with benign results from screening referrals ranges from 1:9.3 to 1:1.1, with a mean of 1 cancer detected per 3 biopsies. Because the sensitivity of the test is between 70% and 90% and the negative predictive value less than 100%, it must be emphasized that a normal mammogram does not rule out breast cancer and any clinically suggestive finding requires a timely evaluation. Also, symptomatic women younger than 45 have a higher rate of false-negative tests, possibly attributable to the increased breast glandularity of premenopausal women.

Even with these acknowledged limitations, early detection of breast cancer is possible and effective in reducing mortality. Therefore, annual screening with mammography and clinical breast examination for women older than 50 has been recommended. The age at which to begin mammography, however, has been controversial. Because BCDDP found that a third of the detected breast cancer cases occurred between ages 35 and 49 and were primarily diagnosed by mammography, the American Cancer Society and American College of Radiology recommend that screening begin with a baseline mammogram between ages 35 and 40 and that annual or biennial mammography begin at age 40. The American College of Physicians (ACP), citing concerns of possible radiation risk, personal and financial costs, lack of evidence, and concern about the high rate of false-positive tests, has not concluded that screening of asymptomatic women in this age group is warranted. When risk factors are present, they feel the benefit of screening “probably outweighs any potential harm.” For women aged 60 to 69 years, the ACP reserves recommendations for screening to individual clinical judgment.

Despite evidence supporting the use of mammography, national data on its use in women older than 50 suggest that only 17% to 41% of women have had a mammogram at some time in their life and that only 4% to 15% of women in this age group receive mammography annually. When women are asked why they do not avail themselves of mammography, a high proportion respond that their physicians do not recommend it to them. A recent survey of physicians in Los Angeles found that only 11% of respondents followed American Cancer Society mammography guidelines. A survey of 509 family physicians in the state of New York found that most

believed mammography to be an effective procedure for detecting breast cancer in its early stages but that only 8% recommended an annual mammogram for asymptomatic women older than 50 years. The major deterrents to its use were concern about its safety and reliability, the low probability of detecting breast cancer with screening, patient acceptance, and cost.

Determining the cost of mammography is complex and involves considering a wide range of factors. The direct cost of mammography ranges between \$25 and \$150, depending on the type of mammogram, the number of views taken, and regional variations in health care costs. There is a growing trend among radiologists to provide mammography screening at reduced prices, which should substantially affect the cost-benefit ratio. In most cities in the US, mammography is now available for less than \$50. Physicians who have avoided referring women for mammography because of its high cost should seek out radiology practices that provide quality mammography at reduced prices. Furthermore, as more women are referred for mammography, the cost per examination should be reduced.

In addition to the direct cost of mammography, there are also many hidden financial and personal costs. These include the cost and risk of follow-up of positive tests and the anxiety created among those with false-positive tests. Recommendations for biopsy vary among medical centers, with an average ratio of malignancy per biopsy in the US of 1:3. While this represents a substantial addition to the overall cost of screening, recent evidence suggests that there is useful prognostic information to be gained from "benign" biopsies. It is generally agreed that women with proliferative benign breast disease have an increased risk of breast cancer, and recent histopathologic studies have found that subcategories of women with pathologically confirmed benign breast disease are at a substantially increased risk of breast cancer. Another risk with screening mammography is that patients or physicians may be falsely reassured by false-negative tests and delay evaluating suggestive lesions. Also, there is some concern that with the increasing use of mammography, physicians and other health care providers may become less skilled and less diligent in their clinical breast examination. It must be stressed that the clinical examination and mammography are complementary procedures and that a normal mammogram does not rule out breast cancer, as its negative predictive value significantly varies with the probability of disease.

Physicians and women also are appropriately concerned about the small but finite risk of radiation exposure. While no level of radiation is without risk, the levels of radiation required for modern mammography range from 0.2 to 0.4 rad (midplane breast view). Extrapolations from high-dose radiation exposure data suggest that radiation-induced breast cancer would develop after a 10- to 20-year latency period in 1 to 8 women per year among 1 million women screened with a single midplane breast view giving a mean dose of 0.2 to 1.0 rad. This risk is much less than many of the normal risks

associated with daily living. Recent evidence also has shown that the risk of breast cancer associated with radiation exposure diminishes with age and is primarily focused in women younger than 30 years.

In summary, several studies have shown that screening mammography with clinical breast examination is effective in diagnosing early breast cancer and in decreasing mortality from breast cancer. It is recommended annually for women 50 years and older by almost all organizations, and evidence exists that it is also effective in reducing mortality in the 40- to 49-year age group. Mammography is underused in the US for several reasons, of which cost and concern about radiation exposure are most often cited by women and physicians. These concerns must be assessed in the context of a disease that will affect 10% of women during their lifetime and for which diagnosis and treatment at an early stage are the most significant determinants of survival. It is important that physicians understand the significant benefits and also the limitations of screening for breast cancer with clinical breast examination and mammography. Further research must be directed towards determining the optimal timing, frequency, and interval of mammography and breast examination in women of varying risk to enable the design of feasible and effective breast cancer screening programs. A large clinical trial of screening for breast cancer is currently underway in Canada. This study will further define the role of clinical breast examinations and mammography in women ages 40 to 59 and will assess whether combinations of risk factors identify subsets of women with different screening requirements.

Though consideration of a formal cost-benefit analysis with respect to mammography is outside the scope of this review, when this method of analysis was applied to the HIP study, the cost per person-year saved was estimated to be less than \$4,000 and the overall net effect of the screening procedure was estimated to be a gain of nearly \$1.5 million. Mammography is one of the most cost-effective preventive measures available to primary care physicians.

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